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Completely OH-Selective $FeCl_3$-Catalyzed Prins Cyclization: Highly Stereoselective Synthesis of 4-OH-Tetrahydropyrans

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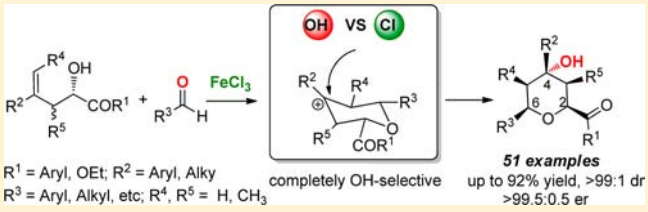
Supporting Information

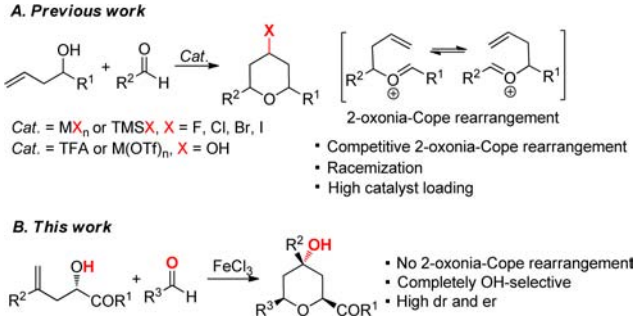
ABSTRACT: The completely OH-selective Prins cyclization has been realized from the enantioselective ene reaction product. A variety of 4-hydroxyl-tetrahydropyrans were exclusively generated via $FeCl_3$-catalyzed Prins reaction. Excellent stereoselectivities (up to >99:1 dr and >99.5:0.5 er) were obtained for a remarkably broad range of substrates under mild reaction conditions. The control experiments, including NOE effects and ^{18}O-labeling studies, as well as DFT calculations were conducted to provide fundamental insights into the mechanism of the reaction. A different [2 + 2] cycloaddition process was suggested to rationalize the observed OH-selectivity.



INTRODUCTION

Substituted tetrahydropyrans represent a common structural motif featured in a large number of natural products and biologically active compounds.[1] In particular, chiral 4-hydroxyl-substituted tetrahydropyran derivatives play an important role in the therapeutic area. In virtue of the varied and significant biological activities[2−4] observed for such a class of compounds, the development of catalytic asymmetric synthesis of 4-hydroxyl tetrahydropyrans is highly valuable. Therefore, a number of reactions have been developed to approach this target.[5] Among the existing approaches, the Prins cyclization, a coupling of a homoallylic alcohol with a carbonyl compound in the presence of an acid catalyst, stood out as one of the most attractive.[6−11] However, the enantioselective access to substituted tetrahydropyrans via the Prins cyclization was restricted to two of the problems common to the typical Prins cyclization protocols: side-chain exchange and partial racemization by reversible 2-oxonia Cope rearrangement and solvolysis effect, which has been demonstrated as a competitive process in Prins cyclization by Rychnovsky and Willis (Scheme 1).[8] On the other hand, in previous works, the halogenated Lewis acid-promoted (such as MX_n and TMSX) Prins cyclizations usually gave the halo-substituted tetrahydropyrans as products, which formed as the result of intermediate trapping by halogen ion (most commonly from the original acid MX_n and TMSX). Also, hydroxyl-substituted products were only obtained as the byproducts.[9] Although hydroxyl-added products could be achieved as the main products in the presence of TFA or $M(OTf)_n$ (a Lewis acid with a non-nucleophilic anion), more generally, strongly acidic conditions and stoichiometric amounts of catalyst were required, affording a mixture of products in some case.[10] Thus, the development of catalytic methods that selectively produce optically active 4-hydroxyl-tetrahydropyrans would be particularly valuable.

Scheme 1. OH-Selective $FeCl_3$-Catalyzed Prins Cyclization



The design of practically simple and efficient organic transformations is one of the main challenges of current organic synthesis. The formation of multiple bonds through sequential reactions constitutes one approach to achieving this goal.[12] Considering the fact that homoallylic alcohols achieved by ene reaction are pivotal substrates for the Prins cyclization, we envisioned that a stepwise catalytic asymmetric ene reaction, followed by an intermolecular Prins cyclization, would produce optically active substituted tetrahydropyrans (Scheme 2). Herein, we report our investigations on the stereoselective synthesis of 4-hydroxyl tetrahydropyrans by sequential ene/Prins cyclization reactions. Chiral Ni(II)−*N*,*N*′-dioxide complex[13,14] and $FeCl_3$ were used for the two processes, respectively. None of the 2-oxonia-Cope rearrangement was observed in the reaction. This new approach permitted an easy and straight route to a range of optically active 4-hydroxyl-tetrahydropyrans with excellent outcomes (up to 92% yield,

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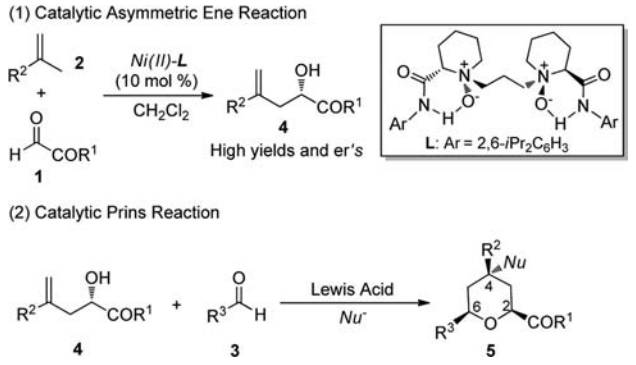
Scheme 2. Lewis Acid-Catalyzed Ene/Prins Cyclizations

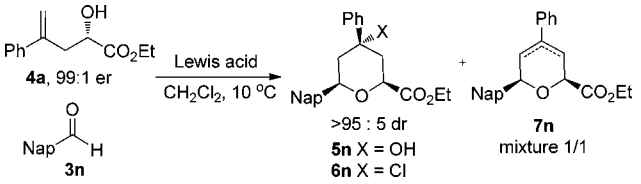


>99:1 dr, >99.5:0.5 er) under mild conditions. We also detailed mechanistic studies such as control experiments, NOE effects, and oxygen-18 labeling studies, as well as computational calculations.

RESULTS AND DISCUSSION

Reaction Optimization. Initially, the chiral homoallylic alcohol **4a** (99:1 er), generated from chiral *N*,*N*′-dioxide **L**–

Table 1. Examination of Lewis Acid in the Prins Cyclization[a]

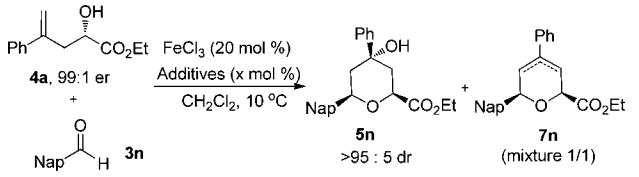


entry	Lewis acid	catalyst loading (mol %)	*t* (h)	yield of **5n**/**7n** (%)[b]	er of **5n**[c]
1	TFA	300	24	36/42	98:2
2	$In(OTf)_3$	20	24	52/32	99:1
3	$Sc(OTf)_3$	20	24	46/35	99:1
4	$AlCl_3$	20	48		
5	$SnCl_4$	20	48		
6	$InCl_3$	20	48		
7	$InBr_3$	20	48		
8	$FeCl_3$	20	24	72/12	99:1
9	$FeBr_3$	20	24	63/22	98.5:1.5
10	anhydrous HCl		6		

[a]Unless otherwise noted, the crude product **4a** (0.2 mmol) obtained from asymmetric catalytic carbonyl–ene reaction was added to a test tube with 2-naphthaldehyde **3n** (0.24 mmol) and acid catalyst in CH_2Cl_2 (1.0 mL) at 10 °C. [b]Isolated yield. [c]Determined by chiral HPLC.

Ni(II) complex catalyzed ene reaction, was used for the Prins reaction with 2-naphthaldehyde **3n**. Various acidic catalysts, generally used in Prins cyclization,[9,10] were examined. To our surprise, 4-hydroxy tetrahydropyran **5n** was exclusively obtained no matter what kind of Lewis acid was used. As shown in Table 1, with 3.0 equiv of TFA, the Prins cyclization proceeded at 10 °C to afford 4-hydroxyl-tetrahydropyran **5n** in 36% yield with 98:2 er, and a 42% yield of dihydro-2*H*-pyran derivatives **7n**[15] (Table 1, entry 1). In the presence of 20 mol % catalyst of $Sc(OTf)_3$ or $In(OTf)_3$ (the Lewis acid with a non-nucleophilic anion), the reactivity was slightly improved, and the product **5n** was obtained in 52% yield and 46% yield,

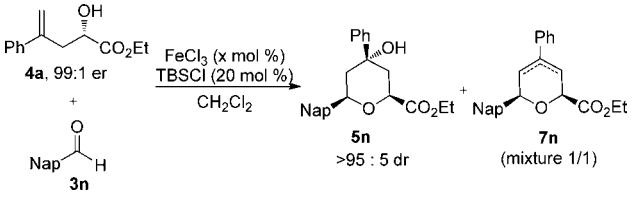
Table 2. Examination of Additives in the Prins Cyclization[a]



entry	additive	*x* (mol %)	*t* (h)	yield of **5n**/**7n** (%)[b]	er of **5n**[c]
1	TMSCl	20	6	<5/68	
2	TESCl	20	6	18/62	99:1
3	TBSCl	20	12	92/<5	99:1
4	Ph_3SiCl	20	24	84/10	99:1
5	TBSOTf	20	0.5	12/65	
6	TMSOTf	20	0.5	<5/72	
7	TBSCl	10	12	90/<5	99:1
8	TBSCl	50	12	92/<5	99:1
9	TBSCl	120	12	89/<5	99:1
10	NEt_3	20	48		
11	H_2O	120	32	89/<5	99:1
12	H_2O	500	64	82/<5	99:1
13[d]	TBSCl	20	48		

[a]Unless otherwise noted, the crude product **4a** (0.2 mmol) of carbonyl–ene reaction was added to a test tube with 2-naphthaldehyde **3n** (0.24 mmol), $FeCl_3$ (20 mol %), and additive (*x* mol %) in CH_2Cl_2 (1.0 mL) at 10 °C. [b]Isolated yield. [c]Determined by chiral HPLC. [d]The reaction was performed without $FeCl_3$. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

Table 3. Optimization of Other Reaction Conditions[a]



entry	conc. (M)[b]	*x* (mol %)	*t* (h)	yield of **5n**/**7n** (%)[c]	er of **5n**[d]
1	0.05	20	32	89/<5	99:1
2	0.1	20	24	90/<5	99:1
3	0.2	20	12	92/<5	99:1
4	0.5	20	10	90/<5	99:1
5	0.2	10	24	89/<5	99:1
6	0.2	50	4	<5/73	
7	0.2	100	1	<5/80	
8[e]	0.2	20	48	87/<5	99:1
9[f]	0.2	20	24	92/<5	99:1
10[g]	0.2	20	4	<5/75	

[a]Unless otherwise noted, the crude product **4a** (0.2 mmol) of carbonyl–ene reaction was added to a test tube with 2-naphthaldehyde **3n** (0.24 mmol), $FeCl_3$ (*x* mol %), and additive (20 mol %) in CH_2Cl_2 at 10 °C. [b]With respect to **4a**. [c]Isolated yield. [d]Determined by chiral HPLC. [e]The reaction was performed at −20 °C. [f]The reaction was performed at 0 °C. [g]The reaction was performed at 35 °C.

respectively (Table 1, entries 2,3). Interestingly, when halogenated Lewis acids, which generally afforded 4-halo-substituted products in previously related work, were tested in the reaction, 4-hydroxy tetrahydropyran **5n** rather than 4-halo tetrahydropyran **6n** was generated.[9] In the presence of 20 mol % of $FeCl_3$, the unexpected hydroxyl-added product **5n** was generated in 72% yield and 99:1 er within 24 h (Table 1, entry 8). Moreover, no competitive 2-oxonia Cope rearrangement

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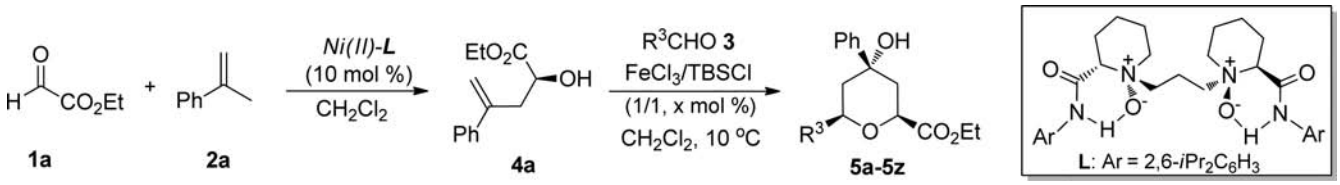
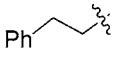
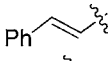
Table 4. Substrate Scope of Aldehydes in the Synthesis of 4-Hydroxyl Tetrahydropyrans[a]



entry	3, R^3	x (mol %)	t (h)[b]	yield (%)[c]	dr[d]	er [c,g]
1	**3a**, C_6H_5	20	12	**5a**, 74	90:10	99:1
2	**3b**, 2-$CH_3C_6H_4$	10	6	**5b**, 85	85:15	99:1
3	**3c**, 3-$CH_3C_6H_4$	10	6	**5c**, 83	90:10	98.5:1.5
4	**3d**, 4-$CH_3C_6H_4$	10	6	**5d**, 88	80:20	99:1
5	**3e**, 2-$CH_3OC_6H_4$	10	4	**5e**, 72	90:10	99:1
6	**3f**, 3-$CH_3OC_6H_4$	10	4	**5f**, 82	85:15	99:1
7	**3g**, 4-$CH_3OC_6H_4$	10	4	**5g**, 90	80:20	98:2
8	**3h**, 4-FC_6H_4	20	24	**5h**, 82	80:20	99:1
9	**3i**, 4-ClC_6H_4	20	24	**5i**, 81	80:20	99:1
10	**3j**, 3-BrC_6H_4	20	24	**5j**, 70	>95:5	99.5:0.5
11[f]	**3k**, 4-BrC_6H_4	20	12	**5k**, 90	>95:5	99.5:0.5
12	**3l**, 4-$CF_3C_6H_4$	20	36	**5l**, 68	>95:5	99:1
13	**3m**, 1-naphthyl	20	16	**5m**, 87	85:15	97.5:2.5
14	**3n**, 2-naphthyl	20	12	**5n**, 92	>95:5	99:1
15	**3o**, 2-furyl	20	12	**5o**, 58	80:20	99:1
16	**3p**, 2-thienyl	20	12	**5p**, 80	90:10	99:1
17	**3q**, Et	10	6	**5q**, 88	99:1	99:1
18	**3r**, *n*-Pr	20	8	**5r**, 85	99:1	99.5:0.5
19	**3s**, *i*-Pr	20	12	**5s**, 84	99:1	98:2
20	**3t**, *t*-Bu	20	24	**5t**, 75	>99:1	97.5:2.5
21	**3u**, *n*-pentyl	20	8	**5u**, 88	>99:1	99:1
22	**3v**, *c*-hexyl	20	24	**5v**, 73	99:1	99.5:0.5
23	**3w**, 	20	24	**5w**, 68	99:1	98.5:1.5
24	**3x**, 	20	6	**5x**, 80	>95:5	99:1
25	**3y**, 	10	3	**5y**, 92	90:10	99:1
26	**3z**, 	20	8	**5z**, 76	99:1	98.5:1.5

[a]Unless otherwise noted, the reaction was carried out with ethyl glyoxylate **1a** (0.2 mmol), 2-phenylpropene **2a** (2.0 equiv), and 10 mol % of Ni(II)−**L** in CH_2Cl_2 (1.0 mL) at 35 °C for 48 h. After flash column chromatography, the crude product **4a** was added to a test tube with aldehyde **3** (0.24 mmol), $FeCl_3$, and TBSCl in CH_2Cl_2 (1.0 mL) at 10 °C. [b]The reaction time of the Prins cyclization. [c]Isolated yield on the basis of **1a**. [d]Determined by ^1H NMR spectroscopy of the crude product and chiral HPLC analysis. [e]Determined by chiral HPLC analysis. [f]The absolute configuration of the product **5k** was determined to be (2*S*, 4*S*, 6*R*) by X-ray diffraction analysis.[19] [g]For most products, the stereochemistry of the minor diastereomer was the same as that of the major diastereomer.[20]

and side-chain exchange occurred. Contrastingly, other Lewis acids such as $AlCl_3$, $SnCl_4$, $InCl_3$, and $InBr_3$ afforded no products, reflecting the importance and particular characteristic of metal iron (Table 1, entries 4−7 vs 8). Changing the counterion of the iron(III) salt provided no improvement in the reaction efficiency (Table 1, entry 9). The anhydrous HCl was also used in the reaction, but no desired product **5n** was obtained, and the reaction only gave some impurity with the same R_f value, which were difficult to separate via flash chromatography (Table 1, entry 10).

These results prompted us to carry out an exhaustive study to find the optimal conditions for the formation of optically active 4-hydroxy tetrahydropyran derivative **5n**. Silicon Lewis acids are a useful mediator in carbon−carbon bond-forming reactions.[16] Inspired by previous works,[9] some acidic compounds such as the TMSCl, TESCl, and TMSOTf as additives were examined to further improve the selectivity and activity of the reaction.[17] As shown in Table 2, it was found that the additives had a significant effect on the outcome of the ratio between **5n** and elimination product **7n**. Excitingly, TBSCl was found as the most effective additive, affording the product **5n**/

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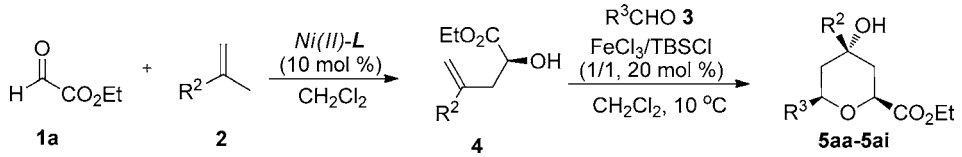
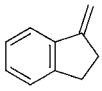
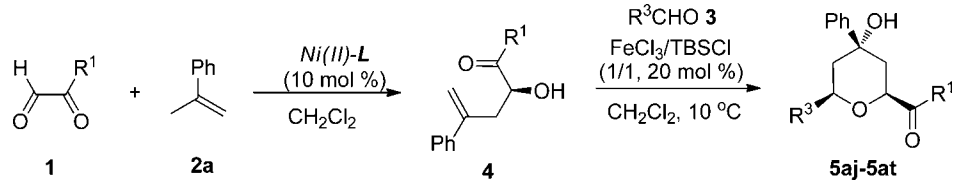
Table 5. Substrate Scope of Alkenes in the Synthesis of 4-Hydroxyl Tetrahydropyrans[a]



entry	2	3	Product 4		Product 5		
			yield (%)[b]	er[d]	yield (%)[b]	dr (%)[c]	er[d,e]
1	**2b**, R^2 = 2-$CH_3C_6H_4$	R^3 = 4-BrC_6H_4	77	99.5:0.5	**5aa**, 50	99:1	98.5:1.5
2	**2c**, R^2 = 4-$CH_3C_6H_4$	R^3 = 4-BrC_6H_4	95	99:1	**5ab**, 58	99:1	99:1
3	**2d**, R^2 = 4-FC_6H_4	R^3 = 4-BrC_6H_4	94	98.5:1.5	**5ac**, 58	90:10	98:2
4	**2e**, R^2 = 4-ClC_6H_4	R^3 = 4-BrC_6H_4	82	99:1	**5ad**, 62	80:20	99:1
5	**2f**, R^2 = 4-BrC_6H_4	R^3 = 4-BrC_6H_4	90	99:1	**5ae**, 52	99:1	99:1
6	**2c**, R^2 = 4-$CH_3C_6H_4$	R^3 = Et	95	99:1	**5af**, 63	99:1	99:1
7	**2d**, R^2 = 4-FC_6H_4	R^3 = Et	94	98.5:1.5	**5ag**, 76	99:1	98.5:1.5
8	**2e**, R^2 = 4-ClC_6H_4	R^3 = Et	82	99:1	**5ah**, 72	99:1	99:1
9	**2f**, R^2 = 4-BrC_6H_4	R^3 = Et	90	98.5:1.5	**5ai**, 75	99:1	98.5:1.5
10	**2g**, R^2 = 4-$CH_3OC_6H_4$	R^3 = Et	95	99:1	-	-	-
11	**2h**, 	R^3 = Et	96	99.5:0.5	-	-	-
12	**2i**, 	R^3 = Et	92	99.5:0.5	-	-	-

[a]The procedure was similar to that in Table 4. [b]Isolated yield based on **1a**. [c]Determined by ^{1}H NMR spectroscopy of the crude product and chiral HPLC analysis. [d]Determined by chiral HPLC analysis. [e]The stereochemistry of the minor diastereomer is unknown.

Table 6. Substrate Scope of Glyoxal Derivatives in the Synthesis of 4-Hydroxyl Tetrahydropyrans[a]



entry	R^1	R^3	product 4		product 5		
			yield (%)[b]	er[d]	yield (%)[b]	dr (%)[c]	er[d,e]
1	Ph	4-BrC_6H_4	98	>99.5:0.5	**5aj**, 65	99:1	>99.5:0.5
2	4-$CH_3C_6H_4$	4-BrC_6H_4	97	>99.5:0.5	**5ak**, 42	99:1	>99.5:0.5
3	4-ClC_6H_4	4-BrC_6H_4	88	>99.5:0.5	**5al**, 48	99:1	99.5:0.5
4	Ph	2-naphthyl	98	>99.5:0.5	**5am**, 56	99:1	98.5:1.5
5	Ph	Et	98	>99.5:0.5	**5an**, 76	99:1	98.5:1.5
6	4-$CH_3C_6H_4$	Et	97	>99.5:0.5	**5ao**, 52	99:1	>99.5:0.5
7	4-$CH_3OC_6H_4$	Et	99	99.5:0.5	**5ap**, 50	99:1	98.5:1.5
8	4-FC_6H_4	Et	92	>99.5:0.5	**5aq**, 58	>95:5	98.5:1.5
9	4-ClC_6H_4	Et	88	>99.5:0.5	**5ar**, 56	99:1	99:1
10	4-BrC_6H_4	Et	95	99.5:0.5	**5as**, 62	>95:5	98.5:1.5
11	2-naphthyl	Et	93	99.5:0.5	**5at**, 58	99:1	97.5:2.5

[a]The procedure was similar to that in Table 4. [b]Isolated yield based on **1**. [c]Determined by ^{1}H NMR spectroscopy of the crude product and chiral HPLC analysis. [d]Determined by chiral HPLC analysis. [e]The stereochemistry of the minor diastereomer is unknown.

7n in 92% and <5% yield, respectively (Table 2, entries 1−6). The enantiomeric excess of the product **5n** was maintained. However, when TMSCl or TESCl was used, the amount of byproduct **7n** exceeded that of **5n** (Table 2, entries 1,2). TBSOTf and TMSOTf shorten the reaction time, but accelerated the generation of the byproduct **7n** (Table 2, entries 5,6). Moreover, varying the amount of TBSCl (0.1−1.2 equiv) had no obvious effect upon the outcomes (Table 2, entries 7−9). The use of base additive NEt_3 inhibited the occurrence of Prins cyclization (Table 2, entry 10). The reaction time was prolonged with an increase of the amount of H_2O, but the elimination product somewhat decreased (Table 2, entries 11,12 vs Table 1, entry 8).[18] Additionally, in the absence of $FeCl_3$, no reaction was observed using TBSCl alone (Table 2, entry 13).

With $FeCl_3$ and TBSCl identified as the optimized catalyst system for the Prins cyclization, effects related to reaction concentration, temperature, and catalyst loading were next

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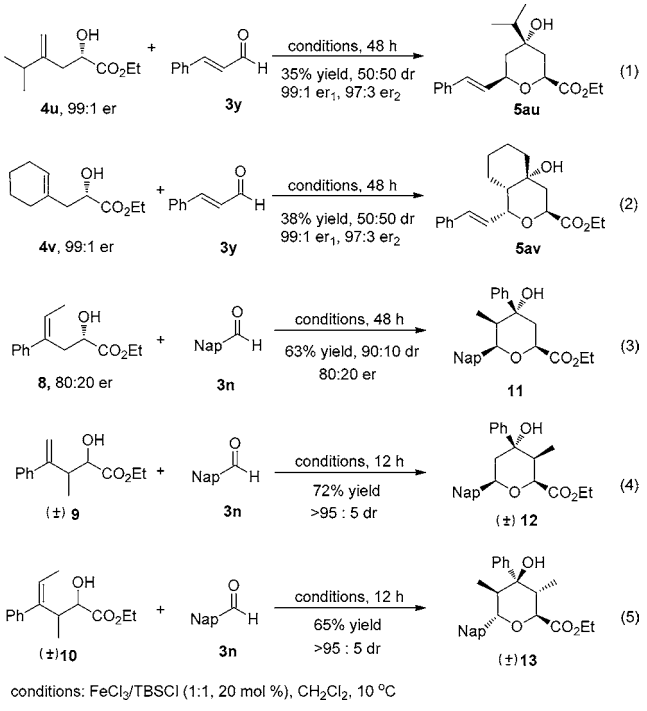
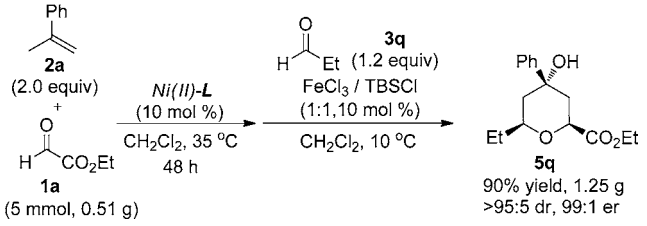
Scheme 3. Substrate Scope of Ene/Prins Cyclization in the Synthesis of Multi-Substituted Tetrahydropyrans



Scheme 4. Asymmetric Ene/Prins Cyclization on a Gram Scale



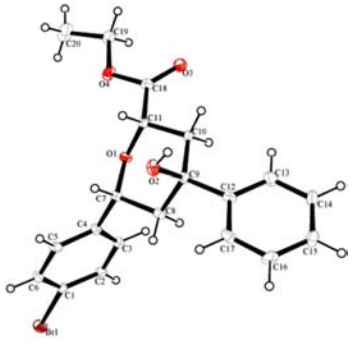


Figure 1. X-ray crystallographic structure of the product **5k**. The thermal ellipsoids' level is 30% for the above crystal structure.

examined. As shown in Table 3, a slight enhancement in reactivity was observed when the concentration was increased (Table 3, entries 1–4). It is worth pointing out that decreasing the catalyst loading to 10 mol % resulted in a slightly reduced yield of **5n** (Table 3, entry 5). However, when large quantities of $FeCl_3$ were present, the elimination product **7n** was obtained as the major product (Table 3, entries 6,7). Additionally, decreasing the reaction temperature to 0 or −20 °C led to no improvements (Table 3, entries 8,9). High temperature was

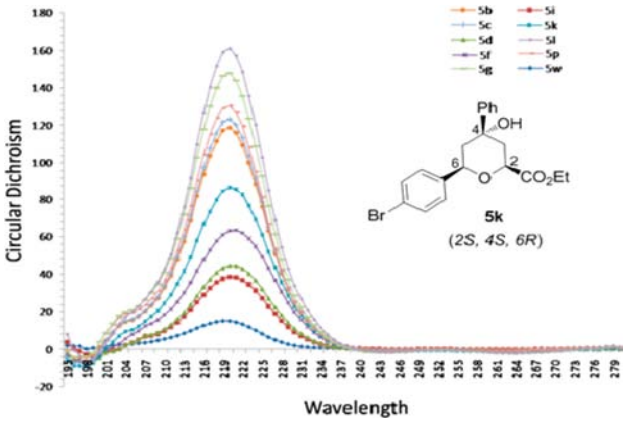


Figure 2. Selected CD (circular dichroism) spectra of a part of the products.

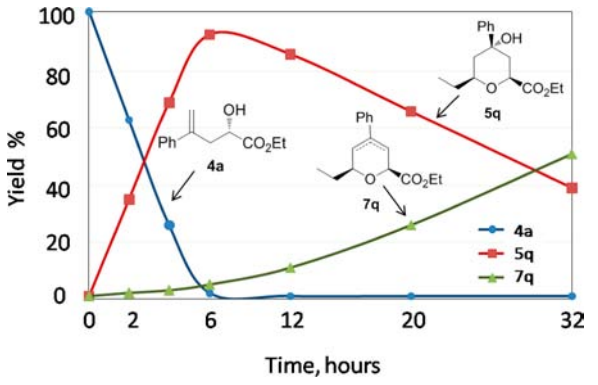
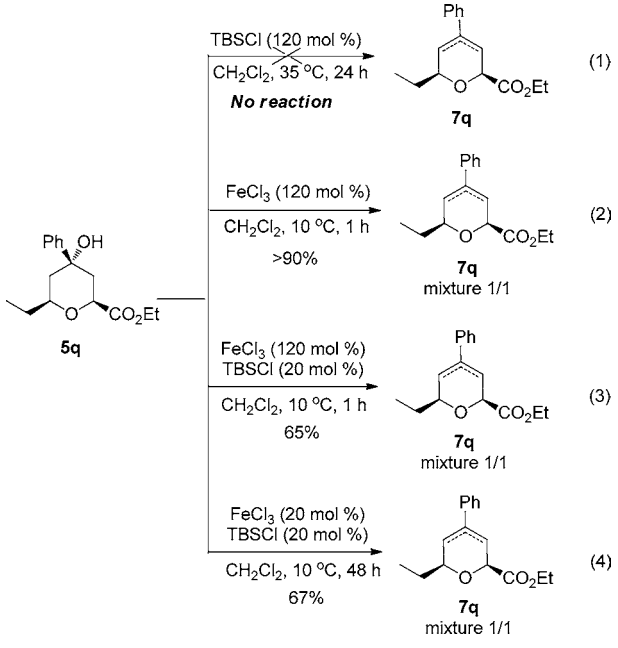


Figure 3. Reaction profile of $FeCl_3$-catalyzed Prins cyclization, picturing the formation and elimination of the product **5q**.

Scheme 5. Elimination Reactions from the Product 5q



favorable for the formation of the product **7n**, and only a trace of product **5n** was obtained at 35 °C (Table 3, entry 10).

Substrate Scope. With the optimal reaction conditions established, the substrate scope was extended. As summarized

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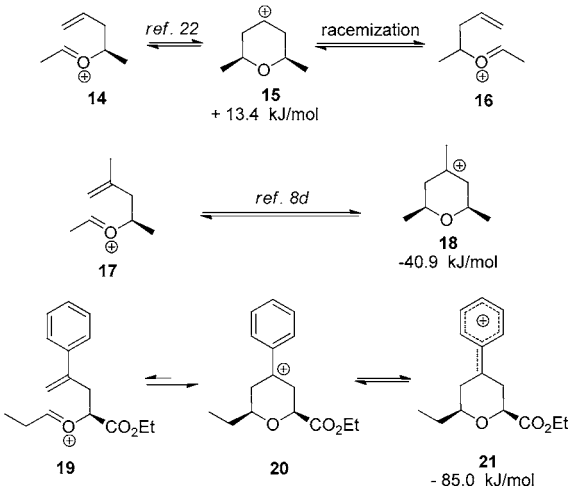
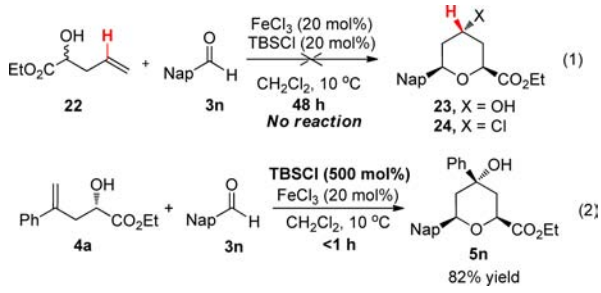


Figure 4. Stabilization of tetrahydropyranyl cation.

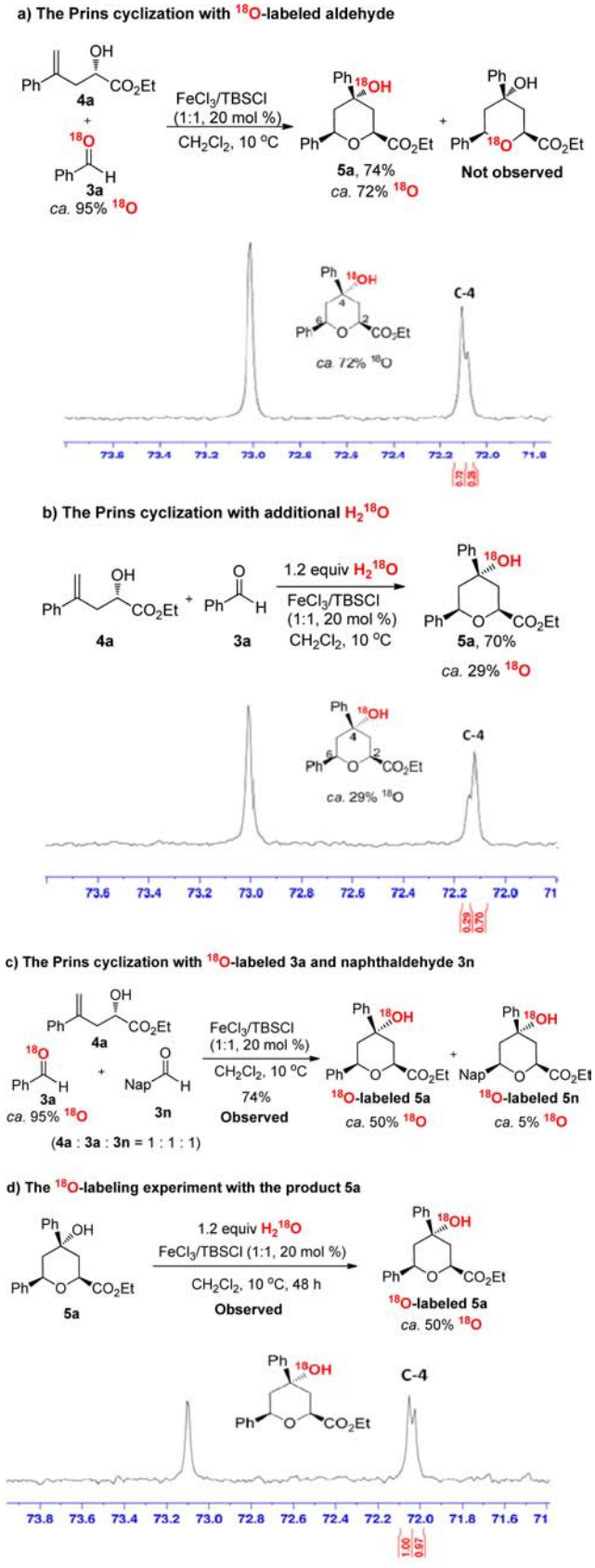
Scheme 6. Control Experiments



in Table 4, the reaction displayed a broad scope for aldehydes, and excellent levels of chemo- and stereoselectivity were achieved. Aromatic aldehydes with either electron-donating or -withdrawing substituents at the *ortho*-, *meta*-, or *para*-positions all performed well, furnishing the corresponding products with 68−90% yields, 80:20 to >95:5 dr, and 98:2 to >99:1 er (Table 4, entries 2−12). In general, the reaction rate of the Prins cyclization was higher with electron-rich aldehydes. For example, methylbenzaldehydes and methoxylbenzaldehydes underwent the reaction within 4−6 h (Table 4, entries 2−7), whereas chloro-, fluoro-, and trifluoromethyl-substituted benzaldehydes required 12−36 h (Table 4, entries 8−12). It was noteworthy that the naphthaldehydes **3m**, **3n**, and the heteroaromatic aldehydes **3o**, **3p** also well tolerated, giving the corresponding products in high yields with excellent stereoselectivities (Table 4, entries 13−16). Some representative aliphatic aldehydes were also evaluated. Excitingly, linear aldehydes, such as *n*-propanal, *n*-butanal, *n*-hexanal, 3-phenylpropanal, cinnamaldehyde, and (*E*)-but-2-enal, gave the corresponding products with high yields within 3−8 h (Table 4, entries 17, 18, 21, and 24−26). Comparatively, steric bulkier aldehydes gave moderate yields with somewhat longer reaction time (Table 4, entries 19, 20, 22, 23). It suggested that for the cyclization of aliphatic aldehydes, smaller steric hindrance significantly benefited the reactivity.

Additionally, a series of alkenes were proven suitable for this reaction as highlighted in Table 5. For the first step, the asymmetric ene reaction of various alkenes (**2b**−**2i**) with ethyl glyoxylate could afford the corresponding homoallylic alcohols **4** in high yields with excellent enantioselectivities (in the range of 98.5:1.5−99.5:0.5 er). As expected, for the following Prins

Scheme 7. Oxygen-18 Labeling Studies of the $FeCl_3$-Mediated Prins Cyclizations and ^{13}C NMR Spectra of the Corresponding Product



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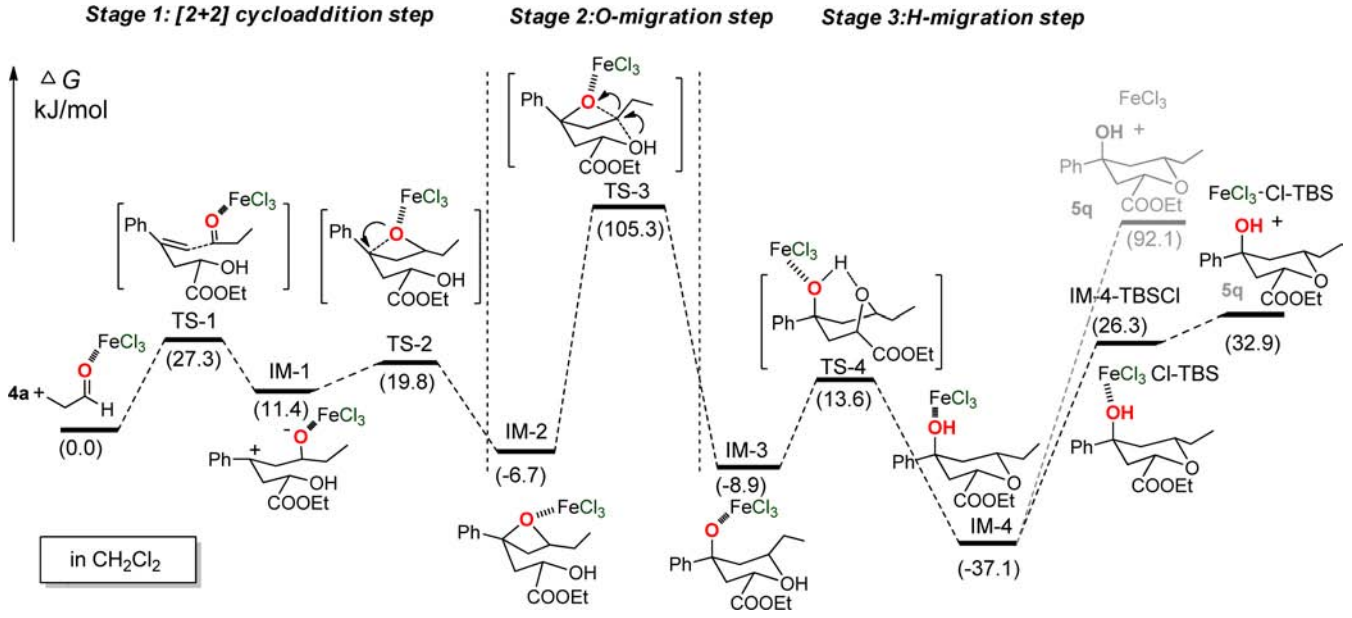

Figure 5. Gibbs free energy diagram and the proposed entire reaction mechanism of the $FeCl_3$-catalyzed Prins cyclization.

cyclization, both aromatic aldehyde and aliphatic aldehyde reacted well with the intermediate **4**, affording the corresponding 4-hydroxyl tetrahydropyrans with moderate to high yields, and excellent stereoselectivities (50−76% yields, 80:20−99:1 dr, 98:2−99:1 er; Table 5, entries 1−9). The electronic nature of the aromatic alkenes had little effect on the yields and stereoselectivities except for the 4-MeO-substituted one (Table 5, entry 10). Both the electron-donating substituted alkenes and the electron-withdrawing substituted alkenes gave the desired products with moderate yields and excellent stereoselectivities (Table 5, entries 1−5). *n*-Propanal gave slightly higher yield as compared to the aromatic aldehyde (Table 5, entries 6−9 vs entries 1−5). It is worth pointing out that, although the ene reaction could give the intermediates **4** with excellent outcomes, no cyclization products were detected if the alkene **2g** with a methoxy group on the aromatic ring or benzocyclic alkenes **2h** and **2i** was used as the starting materials (Table 5, entries 10−12).

Following the studies of asymmetric ene/Prins cyclization with various alkenes, we next examined the scope of the glyoxal derivatives. Unfortunately, the reaction proceeded sluggishly with aromatic aldehydes, and the desired 4-hydroxyl tetrahydropyrans **5aj**−**5am** were obtained in moderate yields (Table 6, entries 1−4). We considered that the steric hindrance effect between the aryl group of glyoxal derivative **1** and the aryl group of the aldehyde **3** increased in the Prins cyclization process, and thus lowered the yield. Accordingly, *n*-propanal was used to minimize this adverse effect. To our delight, the corresponding product **5an** was formed with 76% yield and excellent enantiomeric excess (99:1 dr, 98.5:1.5 er; Table 6, entry 5). Next, the substrate scope of glyoxal derivatives was briefly examined. As shown in Table 6, the electronic nature of the glyoxal derivatives had little effect on the reaction activity and stereoselectivity (Table 6, entries 6−10). The condensed-ring glyoxal also performed well, giving the corresponding product in moderate yield with excellent er ratio (Table 6, entry 11).

To further investigate the potential utility of the reaction, we chose different homoallylic alcohols as the substrates under the standard Prins reaction conditions. The cyclization of alkyl-substituted olefin was investigated. After optimizing the conditions, the cinnamaldehyde **3y** was used to react with alkyl-substituted olefin **4u** and **4v**, and the corresponding products with aliphatic group at the C4 of the THP were obtained with 35−38% yields within 48 h (Scheme 3, eqs 1,2). Besides, the elimination products accompanied the reaction.[21] In addition, when the multisubstituted olefin **8**−**10** were treated with 2-naphthaldehyde **3n** under the standard reaction conditions, the corresponding tetrahydropyrans **11**−**13** with methyl substitutents at 3- or 5-positions were obtained in 63−72% yields (Scheme 3, eqs 3−5).

For the purpose of examining the potential utility of this methodology, a model reaction was carried out on a gram scale. As shown in Scheme 4, the reaction took place smoothly in the presence of 10 mol % of Ni(II)−**L** and 10 mol % of $FeCl_3$/TBSCl, affording a slightly better yield of the product **5q** (90%) without any loss of the enantiomeric excess.

Stereochemical Assignment. It is worth pointing out that in most cases high diastereoselective products were obtained, even single diastereomer for most substrates. The stereochemistry of substituted tetrahydropyrans **5q**, **5m**, **5r**, and **5u** was confirmed by NOE studies,[20] which clearly revealed that three bulky substituents at C-2, C-4, and C-6 on the tetrahydropyranyl ring occupied equatorial positions. In each case, an excellent degree of selectivity was observed for the newly formed stereogenic centers at the 4- and 6-positions of the tetrahydropyran ring. These results were consistent with Alder's computational calculation and previous works.[8,22] Furthermore, the absolute configuration of the product **5k** was determined as (2*S*, 4*S*, 6*R*) by X-ray crystallographic analysis (Figure 1).[19] The CD (circular dichroism) spectra of products were measured in ethanol. Those of 4-hydroxyl tetrahydropyrans exhibited a similar (+) Cotton effect in their CD spectra (as shown in Figure 2).

Mechanism Study. The unique chemoselectivity (completely OH-selective) in the $FeCl_3$-catalyzed Prins cyclization of aldehydes encouraged us to investigate the reaction mechanism. First, we wanted to verify whether the elimination products **7**

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arose solely through eliminating water from compounds **5** or formed via eliminating hydrogen ion directly from the carbocation intermediate. A careful monitoring of the reaction under the standard conditions was investigated. The reaction profile in Figure 3 clearly showed the formation of the product **7q** during the reaction course. The amount of elimination products **7q** increased sharply after 6 h along with the diminution of the product **5q**. It indicated that the product **7** formed more likely through eliminating water from the precursor **5**. To find out the linchpin subject of the elimination process, the catalyst components of Prins reaction were introduced to the isolated product **5q** (Scheme 5). In the presence of 1.2 equiv of TBSCl at 35 °C, **5q** could not transform into **7q** after 24 h (Scheme 5, eq 1). However, the addition of 1.2 equiv of $FeCl_3$ led to a full conversion of **5q** into **7q** within 1 h (Scheme 5, eq 2). The elimination reaction was effectively suppressed (65% yield of **7q** in 1 h) when 20 mol % of TBSCl was added in the reaction (eq 3 vs eq 2). Expectedly, **5q** was slowly transformed into **7q** under the standard reaction conditions (eq 4). These results indicated that $FeCl_3$ mediated both the formation and the elimination of the product **5q**, and the formation of product **5q** was prior to the elimination.[23]

We next tried to rationalize the phenomenon of excellent stereoselectivity of the highly substituted tetrahydropyran products.[8] Relative rates of Prins cyclization versus competing oxonia-Cope rearrangement had a dramatic effect upon the stereoselectivity. Stabilizing the tetrahydropyranyl cation intermediate raised the transition state energy for ring-opening and effectively eliminates oxonia-Cope rearrangement.[8d] Alder's model had shown that oxocarbenium ion **14** is 13.4 kJ/mol stable than tetrahydropyranyl cation **15**. The activation barrier for the ring-opening of cation **15** to oxocarbenium ion **14** is only 1.9 kJ/mol.[22] Thus, the oxonia-Cope rearrangements were rapid for monosubstituted olefins.

To provide insight into the tetrahydropyranyl cation stability in this case, DFT (B3LYP/6-31G*) calculations were performed (Figure 4). In contrast, tetrahydropyran cation **21** was stabilized due to the delocalization of the phenyl group at the 4-position, which is 85.0 kJ/mol lower in energy than oxocarbenium ion **19**. In addition, the oxocarbenium ion resulting from the hypothetical rearrangement was also destabilized. The results were similar to those of Rychnovsky's report, in which the tetrahydropyranyl cation with a methyl group at 4-position **18** is 40.9 kJ/mol lower in energy than oxocarbenium ion **17**.[8d] Therefore, cyclization was irreversible, and the 2-oxonia Cope rearrangement was disfavored than the nucleophilic capture. As a result, oxonia Cope rearrangement-mediated racemization was ruled out.

With an initial survey of reaction stereoselectivity, our attention turned to the chemoselectivity of the reaction that 4-hydroxyl-tetrahydropyran **5** rather than the 4-chloro-substituted one was observed in the $FeCl_3$-catalyzed Prins cyclization. The monosubstituted olefin **22** was used as the substrate to react with 2-naphthaldehyde **3n** under the $FeCl_3$/TBSCl conditions, but no cyclization product was observed with the starting materials being recovered quantitatively after 48 h (Scheme 6, eq 1). The results indicated that the substituent at the C4 position played an important role for the formation of the 4-hydroxyl tetrahydropyran. For the initial substrate **4a**, no trace of chloro-added product was detected even though the amount of TBSCl was increased to 5 equiv. Interestingly, the 4-hydroxyl-tetrahydropyran **5n** was obtained in 82% yield within 1 h (Scheme 6, eq 2). These results indicated that the nucleophile concentration (Cl^- or OH^-) did not affect the selectivity of the reaction. TBSCl might assist the $FeCl_3$-mediated Prins reaction.

To further verify the generation of the reactive hydroxyl nucleophile, as well as the OH-trapped product **5** via solely a direct intramolecular or an intermolecular process, the isotopic labeling experiments were performed. As shown in Scheme 7, the ^{18}O-labeled aldehyde **3a** was used under the standard cyclization conditions, and the product was analyzed by ^{13}C NMR spectroscopy and ESI−MS. It was found that ^{18}O-labeled product **5a** was formed with ca. 72% ^{18}O-labeled solely at 4-position. The corresponding ^{13}C NMR spectrum illustrated apparently a small upfield shift (ca. δ 0.02 ppm) of the signal, assigned to C-4 in each case as a result of the α-isotope effect (Scheme 7a). The result indicated that the oxygen atom of the hydroxy at C4 position of products was transformed from the aldehyde **3a**. In contrast, when 1.2 equiv of $H_2{}^{18}O$ was added under the standard conditions, the 4-hydroxyl-tetrahydropyran **5a** was formed with ca. 29% ^{18}O-labeled (Scheme 7b). We also found that the ^{18}O-labeled product **5n** was observed excepted for the ^{18}O-labeled product **5a**, when olefin **4a** was added to the mixture of the ^{18}O-labeled benzaldehyde **3a** and ^{16}O-labeled naphthaldehyde **3n** with the catalyst $FeCl_3$/TBSCl (Scheme 7c).[24] Moreover, the ^{18}O-labeled product **5a** (50% ^{18}O-labeled) was also observed when the product **5a** was treated with 1.2 equiv of $H_2{}^{18}O$ under the standard reaction conditions (Scheme 7d). These results suggested that the products **5** were more likely to be formed through an intramolecular way. The hydroxyl group at C4 position might exchange with the OH^- from the reaction system under the standard reaction conditions via carbonium ion intermediate.

To provide further insight into the observed OH-selective process of 4-phenyl tetrahydropyran catalyzed by $FeCl_3$, DFT (B3LYP(PCM,CH_2Cl_2)//B3LYP/6-31G**) calculations were performed.[20] A different Prins cyclization mechanism was suggested. The results of calculations related to the entire reaction mechanism were illustrated in Figure 5. It is shown that the entire catalytic cycle contains three successive stages: (1) stepwise [2 + 2] cycloaddition reaction via **TS1** and **TS2**; (2) migration of O atom of acetaldehyde to **4a** with the cleavage of C−O bond of the carbonyl group via **TS3**; and (3) migration of H of −OH in **4a** via **TS4**, leading to the formation of **5q**. PCM calculation placed the largest barrier in Gibbs free energy to be 112.0 kJ/mol, which corresponds to the step from **IM2** to **TS3** in stage two. This step is rate-determining in the entire reaction process. Moreover, the calculation predicted that the O atom of −OH in **5q** comes from acetaldehyde and H from **4a**, respectively. It also showed that the release of $FeCl_3$, corresponding to **IM4** to $FeCl_3$+**5q**, must overcome a significant large energy barrier of ca. 140 kJ/mol, which is comparable to the barrier of RDS. This means that the catalytic cycle would be hindered in the step of recovery of $FeCl_3$ if no other auxiliary reagent is involved.

However, when TBSCl is considered, DFT calculations predicted that TBSCl might coordinate to the $FeCl_3$ with the formation of TBSCl−$FeCl_3$ species form **IM4**, resulting in the yield of **5q** with a smaller energy barrier of 70.0 kJ/mol. Therefore, the existence of TBSCl might facilitate the formation of **5q** and exert a positive effect on the present $FeCl_3$ catalytic systems.[23] This theoretical prediction is in agreement with the present experimental observation. In previous works, the general mechanism of Lewis acid catalyzed Prins cyclization is that the key intermediate is an

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oxocarbenium ion, which was generated from a hemiacetal. Next, the oxo-carbenium ion could be captured with a large array of nucleophiles to afford substituted tetrahydropyrans. The nature of such a difference between the two mechanisms is not yet clear at present. It might be due to the variation of catalysts as well as the homoallylic alcohols used in the reactions.

CONCLUSION

We have established a general method for the completely OH-selective sequential ene/Prins cyclization by using Ni(II)–*N*,*N*′-dioxide complex and $FeCl_3$ as the catalysts, respectively. The method enabled an efficient access to optically pure 4-hydroxyl-tetrahydropyran derivatives. The extremely high enantiomeric excess, broad substrate scope, facile procedure, and mild reaction conditions showed the potential of the catalytic system for practical synthesis. This method will be a valuable complement to the existing arsenal of the enantioselective synthesis of 4-hydroxyl tetrahydropyrans via Prins cyclization. Moreover, mechanistic investigations including control experiments, NOE effects, oxygen-18 labeling studies, DFT calculations were also investigated to gain insight into the mechanism of the reaction. Additional investigations aimed at expanding the scope of the application are underway.

EXPERIMENTAL SECTION

Typical Experimental Procedure for the Sequential Ene/Prins Reaction. A mixture of *N*,*N*′-dioxide L (12.8 mg, 0.02 mmol) and $Ni(BF_4)_2{\cdot}6H_2O$ (6.8 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) was stirred at 30 °C for 30 min. Next, the ethyl glyoxylate **1a** (0.2 mmol) and 2.0 equiv of 2-phenylpropene **2a** were added at 35 °C and stirred for 48 h. After flash column chromatography, the crude product of the carbonyl–ene reaction was added into the test tube with 1.2 equiv of 2-naphthaldehyde **3n** (0.24 mmol), 20 mol % of $FeCl_3$, and 20 mol % of TBSCl in CH_2Cl_2 (1.0 mL) at 10 °C. After being stirred at 10 °C for 12 h, the reaction mixture was directly purified by column chromatography on silica gel (ethyl acetate:petroleum ether = 1:8) to afford the corresponding product **5n** in 92% yield as a colorless liquid. The enantiomeric excess of **5n** was determined by using chiral HPLC analysis.

ASSOCIATED CONTENT

Supporting Information

Experimental details and analytic data (NMR, HPLC, and ESI-HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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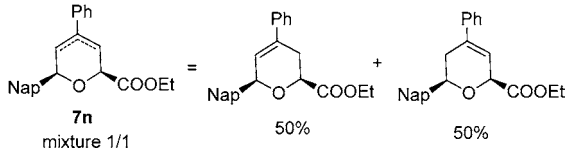
(15) The product **7n** was always obtained as a mixture (1/1) of two inseparable dihydropyrans, and the combined yield was given.



7n
mixture 1/1
50%
50%

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(17) Other additives such as $PhCO_2H$, PhOH, TMSOH, and TMSH were also examined, but no better results were obtained.

(18) The clarified reaction solution became turbid, generating brown viscous compounds on the tube wall when H_2O was added. It might be the hydrolysis of $FeCl_3$.

(19) CCDC 855357 contains the supplementary crystallographic data for this Article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) For more data, see the Supporting Information.

(21) The separation of them from the reaction mixture was difficult via flash chromatography as the elimination products have the same R_f value as the cinnamaldehyde **3y**.

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(23) The role of TBSCl in suppressing the eliminated products is uncertain at present. The reactivity of R_3SiCl is different by varying the steric volume of alkyl substituents, which might lead to the contrast results by the use of TMSCl and TESCl.

(24) The separation of pure **5a** or **5n** from the reaction mixture was difficult via flash chromatography due to that they have the same R_f value. The mixture of **5a** and **5n** was analyzed by ESI−MS.